Measuring the force of sound

MECHANOCHEMISTRY

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The mechanical action of ultrasound on small, functionalized molecules (mechanophores) embedded in a polymer chain often enables unusual chemical transformations. There is now a systematic effort to quantify the reactivity of mechanophores.

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Chemists always dream of achieving quantitative relationships and look for predictive behavior and sound theories. This is not an easy goal. For example, Richet reported in 1893 that the narcotic action of some organic compounds was inversely related to their water solubility[1], however, it took nearly 70 years to find the first relationship between bioactivity and molecular descriptors[2].

Correlations are particularly challenging in some emerging fields, especially when they describe complex physico-chemical phenomena, and this is certainly the case for mechanochemistry; a discipline which uses the enormous potential of tensile forces to perform chemical reactions and design mechanoresponsive materials[3]. Writing in the *Journal of the American Chemical Society*, Moore and co-workers describe a method of assessing structure-mechanochemical activity relationships (SMARs) in an acoustic field[4], in an attempt to simulate the classic QSAR approaches that link the biological action of pharmacophores to their structures.

Ultrasound waves (i.e. sound with frequencies higher than 16 kHz) of sufficient intensity passing through a liquid generate cavitation bubbles that quickly grow and collapse. The chemical excitation of volatile molecules inside such microcavities, coupled with the shock waves and shear forces caused by bubble implosion, can be harnessed to promote chemical reactions[5]. Solvated polymer chains near the growing bubbles function as molecular tweezers that convey significant tensile forces to mechanophores placed at the center of the chain. , Moore and associates chose cyclobutanes of variable stereochemistry and substitution patterns to carry out this role, as these molecules are sonochemically cleaved via a formal retro [2+2] cycloaddition to give alkenes.

How did the team predict relative chemical reactivity under the mechanical action of sonication? The toehold here is a computational method invented by Beyer—constrained geometries simulate external force (CoGEF)—in which mechanical deformation, at the molecular scale, is simulated by constraining the distance between two atoms of the mechanophore and then sequentially elongating the same distance[6]. To alleviate the computational load, theoretical modeling was conducted on methyl esters derived from six *cis* and *trans* cyclobutane

mechanophores with two, one or no cyano substituents (DCC/DCT, MCC/MCT and NCC/NCT pairs, respectively) as depicted in Figure 1.

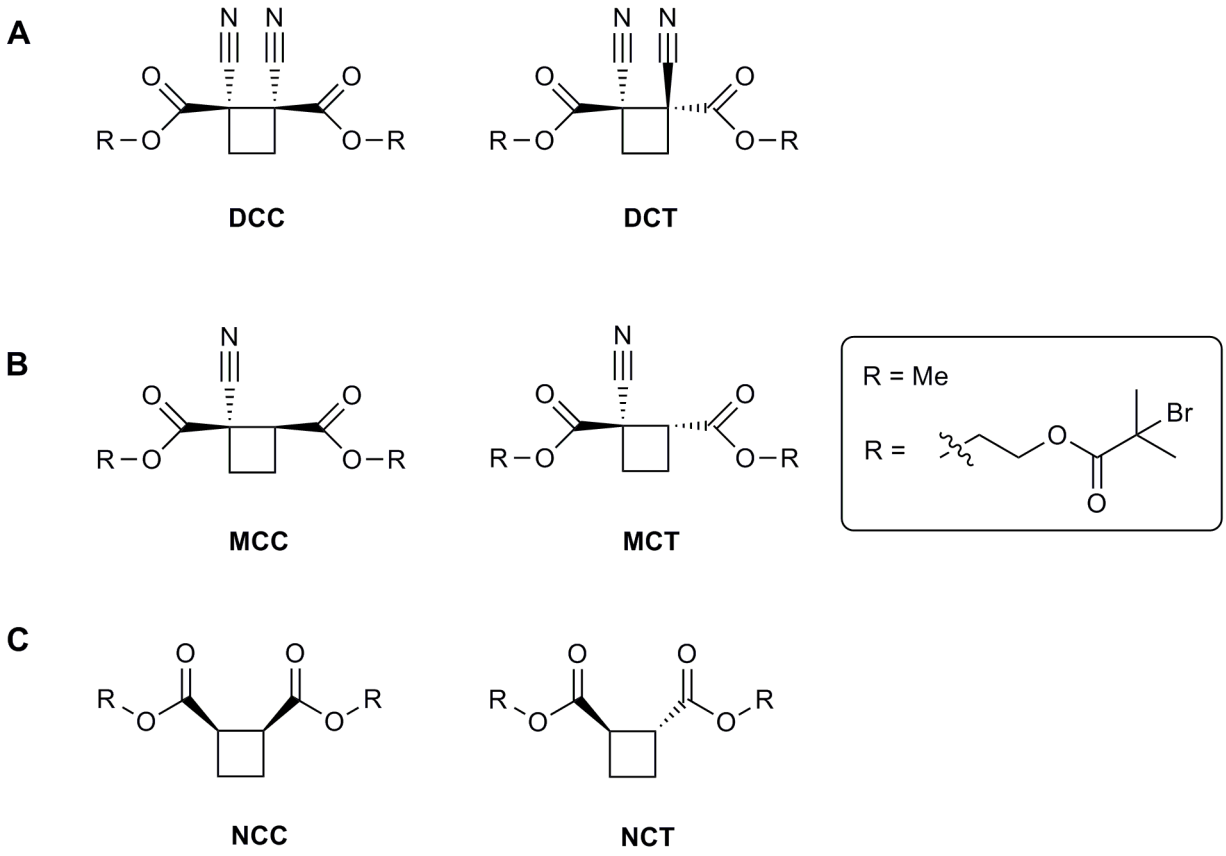

Figure 1| Structural series of cyclobutane mechanophores: (A) *cis* and *trans* dicyano-substituted cyclobutanes (DCC and DCT); (B) *cis* and *trans* monocyano-substituted cyclobutanes (MCC and MCT), and (C) *cis* and *trans* cyclobutanes without cyano substituents (NCC and NCT). Cyanocyclobutane mechanophores amount to masked cyanoacrylates that can be unveiled using sonication. Pendant esters include methyl groups for theoretical calculations as well as α-bromoisobutyryl derivatives as polymerization initiators

DFT-based CoGEF calculations revealed two salient trends; a) the *cis* mechanophore was more reactive than the *trans* isomer (in other words, less force is required to obtain bond rupture), and b) mechanophore reactivity increases as cyclobutante substitution increases, which presumably arises from enhanced ring strain caused by steric interactions. Gratifyingly, these predictions were corroborated even when the mechanophores were embedded in poly(methyl acrylate) (PMA) polymers, of molecular weights ranging from 35 to 125 kDa, which were grown by single-electron-transfer living-radical polymerization after installing the corresponding pendant α-bromoester initiators (Figure 1).

Upon sonicating all the members of this polymer molecular weight series, with the addition of two control polymers, (one a PMA homopolymer containing neither a center-based

mechanophore nor an alkane and the other where the cyclobutane ring was replaced with an alkane bridge) the authors were able to measure and compare the relative rates of mechanophore scission under ultrasound. These results can be plotted as linear relationships of *k* (rate constant of polymer cleavage) *vs* M_i (initial average molecular weight). Notably, the changes in molecular weight threshold were markedly distinct for the different mechanophore-containing polymers. In close mimicry of the computational study, the *cis* derivatives were more reactive than the *trans* counterparts for a given substitution level. Secondly, the more highly-substituted mechanophores underwent faster scission than the less-substituted ones (Figure 2). The control polymers were less reactive in the acoustic field than the cyclobutane mechanophores with the sole exception of the NCT ring.

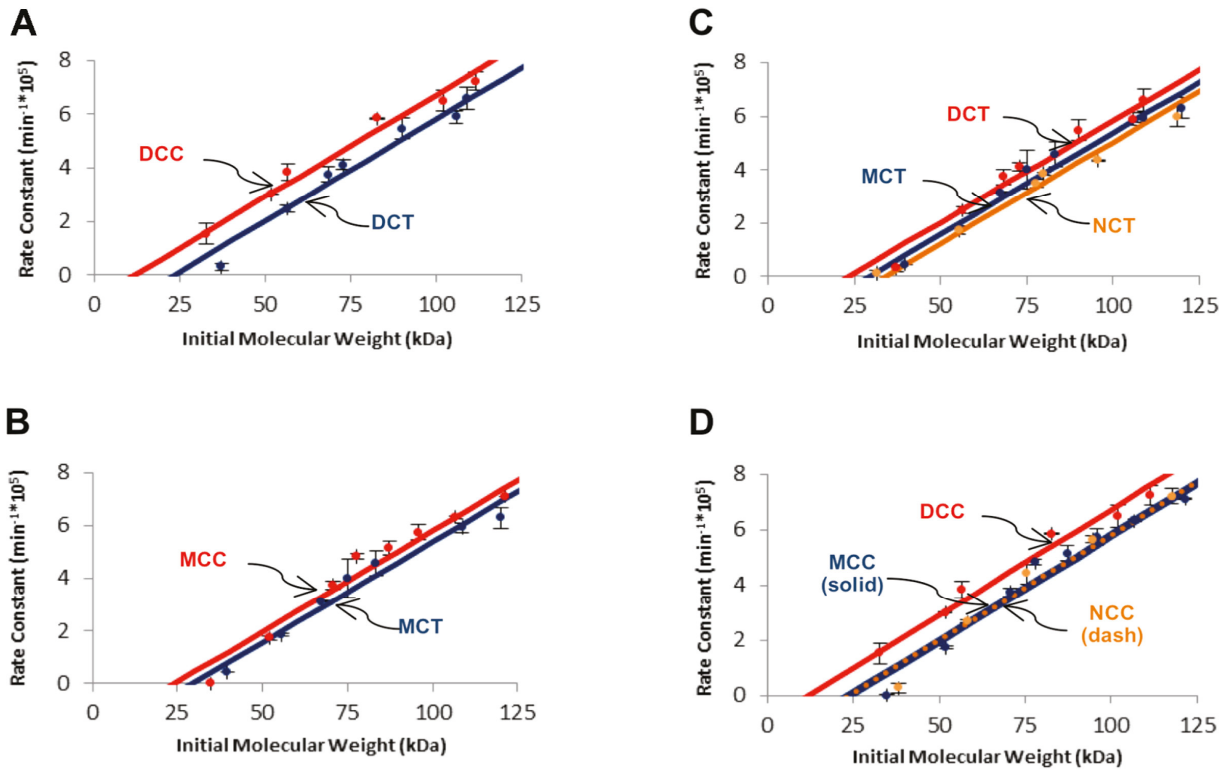

Figure 2| Plots showing the linear relationships between experimental polymer scission rate constants and initial polymer molecular weights. (A) Cleavage of DCC (R^2 = 0.974) and DCT (R^2 = 0.962) polymers, (B) cleavage of MCC (R^2 = 0.958) and MCT (R^2 = 0961) polymers, (C) cleavage of DCT, MCT and NCT polymers, (D) cleavage of DCC, MCC and NCC polymers. Adapted and reproduced with permission from Ref. 4. Copyright 2011 by the American Chemical Society.

This work raises additional questions and challenges regarding the nature of force and its effect on mechanophores. The extent of cavitational collapse, and hence the associated mechanical action, are dependent on numerous parameters; especially solvent properties and ultrasound frequency and intensity (an increase in the latter will also provide for an increase in

sonochemical effects). Accordingly, selective cleavage or mechanophore activation will require optimum values for almost all variable parameters. On the other hand, mechanical activation of a particular small molecule may occur via a mechanism other than scission and will therefore require different modeling. This drawback was also highlighted by Moore and co-worker. Therfore, other chemomechanical formalisms can help to establish a quantitative relationship between a macroscopic descriptor of external force and rates of varying chemical reactions such as solvolysis, isomerization, or substitution to name a few[7]. Finally, a relevant issue concerning the effect of stretched polymers on mechanophores is found in the entropic contribution. While the latter may be negligible for small and rigid molecules that exist as a single conformer, the conformational heterogeneity may alter the mechanical energy-transducing pathway[8].

Although the strategy outlined by Moore and his team is still far from a mathematical algorithm describing the dependence of force on structural, electronic or topological descriptors, the importance of this work lies in showing that there is actually a molecular basis for SMARs. More importantly, the application of mechanical forces in the case of biomolecules and mechanophores of pharmaceutical interest may eventually lead to the accurate rationalization of the specific action of ultrasound on such systems.

Preliminary, yet stimulating, as it is, the present work by Moore and associates should now really stimulate a further jump in mechanochemical studies.

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